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Current Opinion in Behavioral Sciences

Cognitive remediation in schizophrenia — now it is really getting personal

Matteo Cella, Clare Reeder and Til Wykes

Cognitive problems are consistently documented in people with schizophrenia. They negatively influence functioning and contribute to the long term consequences of the illness. Cognitive remediation (CR) is a psychological intervention developed to target these cognitive difficulties. There is evidence that CR is beneficial but there is still a limited understanding of how the putative active therapy ingredients contribute to changes in the brain and translate into improved functioning. This paper reviews recent research focused on topics that, in our view, will drive future developments such as the identification of translational mechanisms, the personalisation of CR, the best implementation methods and potential augmenting strategies to improve treatment effectiveness.

Address
Department of Psychology, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK

Corresponding author: Cella, Matteo (matteo.cella@kcl.ac.uk)

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Introduction

In schizophrenia cognitive problems precede illness onset and are evident from an early age [1,2]. These deficits are associated with functional outcomes and are considered rate limiting factors for recovery, even when high quality rehabilitation is provided [3]. This was the driving force behind the development of behavioural training aimed at treating cognitive difficulties in people with psychosis [4]. These programmes are referred to under the umbrella term of cognitive remediation (CR) or cognitive training. There is now overwhelming evidence that CR is modestly effective in improving cognition and functioning but what is not clear is how it should be provided, to whom, in what doses and how we can boost its effects. There are many reasons for this lack of knowledge but here we consider what we do know that can aid personalisation using the latest literature on the potential underlying mechanisms, the treatment context for boosting effects and which patients benefit the most and for whom are current systems ineffective.

A consensus on CR

Increasing efforts have been made to define what constitutes CR. This is particularly important in light of recent claims suggesting that CR programmes improve work performance or slow brain ageing. These claims, as the scientific community has pointed out, are largely speculative and not supported by strong evidence [5,6]. In fact a large population based study [7] showed that it only improved performance on the tasks trained and did not generalise to cognitive functions. The lack of support for commercial companies' promises prompted a reflection from the scientific community on the definition of CR. Questions such as 'what are the active components and treatment targets?' are increasingly central to a full understanding of CR's potential. CR applications to mental health problems are relatively common [8••,9]. For psychotic disorders the Cognitive Remediation Experts Working group defines CR as: 'a behavioural-training based intervention that aims to improve cognitive processes (i.e. attention, memory, executive function, social cognition, or metacognition) with the goal of durability and generalization' where social cognition is defined as 'the mental operations that underlie social interactions including perceiving, interpreting, and generating responses to the intentions, dispositions, and behaviours of others'.

Two 'schools' of CR have dominated the field. The drill and practice approach which proposes that cognitive improvement can be obtained primarily by frequent and intensive task practice tailored to the individual's ability. The alternative approach suggests that tasks practice should be supplemented by strategy use to increase the potential for generalisation to real world problems. This distinction is similar to the distinction between 'top-down' or 'bottom-up' approaches. Top-down programmes preferentially target higher order cognitive functions, such metacognition and executive function, and encourage a strategic approach to task practice. Bottom-up approaches tend to preferentially train basic attentional and perceptual skills. The growing consensus is that they may not be as distinct as previously thought [10]. Studies of moderators and mediators of the treatment effects will contribute to clarifying the role of intensive training and strategy use but also to characterise the active building blocks of CR.

What is the mechanism underlying the treatment effect? Integrating explanations

Despite consensus on neuroplasticity being an important factor there is still limited evidence on how CR can or

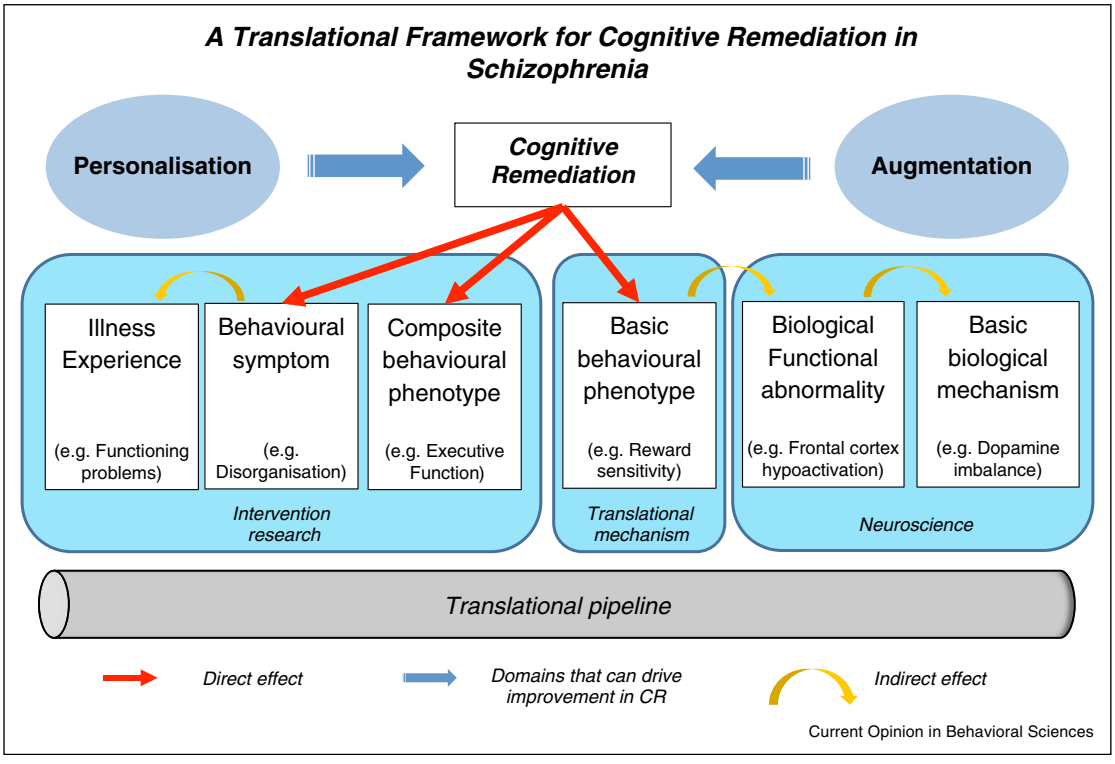
does enhance this process. Evidence from human studies is still scarce but studies conducted in non-human primates suggest that cortical reorganisation may have a unique relationship with task practice [11•].

CR has been shown to improve frontal activity [12], prevent grey matter decay [13], improve brain network efficiency [14•] and task-related blood flow in frontotemporal areas [15]. These are important, but mainly unremarkable, findings as it is unlikely that cognitive improvement could occur without change in the way the brain functions, although preventing grey matter loss is a surprising benefit. However, we still lack a precise understanding of how CR programmes produce these brain effects as they were achieved with different programmes, different numbers of sessions, with and without a therapist.

The application of a translational framework to CR research may overcome this problem (see Figure 1). The dopamine hypothesis of schizophrenia has been the single most influential theory in our understanding of the neurochemical basis of schizophrenia. The hypothesis assumes that psychotic symptoms, such as hallucination and delusions, are caused by a hyperdopaminergic state associated with increased phasic activity in subcortical regions [16]. We know that the dopamine system is also responsible for key cognitive and emotional processes such as motivation, hedonic response and learning [17•] and these features are correlated with perturbation in the prefrontal cortical regions. By identifying behavioural correlates related to these effects we can link biological abnormalities with cognition and define intervention targets. Reward learning (RL) is one such cognitive process which is responsible for proficiency in a variety of tasks and is implicated in learning, motivation and pleasure experiences. There is consensus that prefrontal cortical regions are important in mediating this process and that people with schizophrenia have very specific difficulties in accomplishing tasks requiring RL [18]. Basic studies conducted on animals and healthy volunteers have linked RL and cognitive training with brain neuroplastic changes and alteration in dopaminergic action [19,20]. More recent animal models and pilot clinical trials also suggest that glutamatergic and GABAergic systems may be relevant targets to improve cognition in people with schizophrenia and may be associated with RL processes [21,22]. However, evidence in this area is scarce and mostly based on animal studies.

RL is particularly difficult to track but novel computational methods applied to complex and detailed responses from cognitive tasks do now allow us to surface elements of RL relevant to improved cognitive performance. In a

Figure 1



A translational research framework that can be applied to CR (square text boxes) and methods that can be used to improve CR effectiveness on translational stages (round text boxes).

recent study using these techniques we demonstrated that CR significantly improves sensitivity to reward and negative feedback [23••]. These results demonstrate, for the first time, that a course of behavioural training based on extensive practice and strategy use has an effect on a core feature of schizophrenia — impaired RL. Behavioural research suggests that by acting on the reward system we may be able to target other important features of the illness such as poor motivation and anhedonia [24]. Clearly more work is needed to explore the components of CR more likely to affect RL and how improvements in this domain translate into recovery milestones for patients. However, these findings are promising and may lead to a more integrated understanding of how CR influences brain plasticity.

Boosting treatment effects through CR augmentation

The metaphor of the brain as a muscle and CR as gym training has prompted psychopharmacological research to explore agents that may work as 'brain steroids' for cognition (also referred to as procognitive agents). The number of cognitive enhancing drugs has recently increased opening up the potential for combining behavioural and pharmacological treatments for cognitive problems in schizophrenia [25,26]. This is based on the steroids and training metaphor. But it is not at all clear that the key elements of CR are based solely on task practice. More recent models use pedagogical knowledge which tends to downgrade practice and foreground metacognitive aspects of CR, for instance in the recently developed CIRCuiTS programme [27]. This may be why the field of pharmacological interventions has been disappointing. For instance, Cain *et al.* [28] conducted one of the first RCTs augmenting CR with a D-cycloserine to improve its effect on memory. But only trained tasks improved and this did not generalise to cognitive performance. Modafinil also showed effects on task learning but no generalisation in healthy volunteers and neither effect in people with schizophrenia [29,30]. A further two studies augmenting social cognition training with oxytocin also showed limited or no benefits compared to the placebo [31,32]. All these studies used mainly task practice with no strategy instruction. These negative results suggest an investigation of potential moderators of action not least the type of patients and the type of CR provided. Many studies (but not all) were relatively short and using the blunt instrument of cognitive tests may never have found subtle changes in performance across the varying cognitive profiles of the participants. Without a more personalised approach it is likely that we will miss important signals from adding procognitive drugs. More promising studies, however, are emerging using neuromodulation approaches. For example, repeated applications of transcranial direct current stimulation demonstrate increased cortical excitability and plasticity [33]. To date there are no controlled studies using this method in combination with CR in people with schizophrenia but preliminary evidence from case studies shows encouraging results [34] (see Table 1).

Unlike pharmacological augmentation, combining CR with other behavioural interventions has shown more positive results. The underlying rationale is that cognitive improvements need to be exercised and that other rehabilitation programmes provide this opportunity. For example, CR is most effective in achieving functional outcomes when delivered in combination with supported employment [35,36••]. CR has also been combined with other psychological therapies and demonstrated boosted outcomes, for example, Lindenmayer *et al.* [37]. A recent RCT combining CR with cognitive behavioural therapy (CBT) compared to an active control [38•] showed a reduction in the number of CBT sessions to achieve the same outcome. These studies suggest the possible cost benefit of combining CR with other treatments.

Studies have also explored the potential benefits of combining CR with physical exercise. Aerobic exercise has been associated with increased production of brain neurotropic factor and increased synaptic plasticity [39]. Preliminary studies exploring the effects of physical exercise alone in people with schizophrenia yielded encouraging results suggesting that this intervention alone may be able to increase hippocampal volume [40]. This technique would also promote other general health benefits which for people with schizophrenia might contribute to reduced mortality risk [41].

These findings suggest that CR exerts its maximal benefit when delivered in the context of other rehabilitative interventions but not with additional cognitive enhancing or pro-cognitive drugs. It is still uncertain whether any of these combination studies could have increased benefits when more tailored to individuals — identifying subgroups might also allow us to see signals with pharmacological augmentation.

Table 1

Current evidence in support of augmentation and boosting methods for CR

	Augmenting and boosting CR	
Method	Example	Results
Medication	D-Cycloserine, modafinil, oxytocin	Disappointing
Neuromodulation	Transcranial direct current stimulation	Not enough evidence
Vocational support	Supported employment	Supported by evidence
Psychological therapy	Social cognition, CBT	Promising
Physical exercise	Aerobic activity programme	Not enough evidence

Personalising CR

Identifying characteristics that indicate the most treatment benefit is not only important for individuals but also for the rational allocation of resources in health care. These concepts are therefore increasingly used in treatment research and the field of CR is no exception. The identification of personalising factors has now become complex with interactions between genotype, medication and CR that seem to influence treatment responses. For instance individuals receiving clozapine showed cognitive improvement after a course of CRT independently from their genotypic profile [42]. However, those with the val/val variant of the COMT gene who did not receive clozapine did not show an improvement. A similar study showed an association between a set of nucleotides of the COMT gene and improvement in global cognition following CR [43].

Benefits seem to be larger in younger participants [44] and this might be explained in terms of windows of neuroplastic sensitivity so that targeted training at an early stage of the disorder may achieve larger changes [45]. Cognitive reserve has also been identified as a potential predictive factor [46] as this determines the individual's learning potential. Finally, functional status at intake to CR has also been shown to be an important stratification variable as those with the poorest functioning seem to derive the most benefit from a combined CR plus supported employment treatment [35]. Many of these characteristics have been indicated post hoc in secondary analyses on relatively small samples. The forthcoming Database of Cognitive Training and Remediation Studies (DoCTRS) set up by NIMH should provide larger datasets to examine these potential beneficial (and detrimental) characteristics for CR.

Conclusions

CR techniques have positive, but modest, effects on cognitive difficulties in people with schizophrenia but it remains the only targeted intervention available for cognitive problems [47••]. It has considerable advantages including safety, acceptability and, in association with other rehabilitative approaches, the promotion of recovery. The personalisation agenda has started to form advanced by secondary analyses of (usually) non-significant results [48]. But many of these findings are not grounded in theory and this is where there needs to be more focus. Future studies can then begin to clarify the active therapy mechanism that fosters neuroplasticity and which will lead to durable effects on recovery. There is also a need to conduct more research bridging the gap between clinical practice and basic neuroscience. We have proposed a model highlighting some translational stages that may help researchers and clinicians to incorporate the next level up or down in their research (Figure 1). We hope this framework will contribute linking our knowledge of biological mechanisms to therapy procedures and guide the future developments of CR.

Conflict of interest

None.

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